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REVIEW ARTICLE

A Review of Oral Hypoglycemic Agents

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THIS review of the oral hypoglycemic agents is intended only as a broad outline and guide for use in the treatment of diabetic patients.

The discovery of these agents has stimulated a renewed interest in diabetes mellitus with a concomitant increase in research activity throughout the world by biochemists, physiologists, histopathologists and others working in diabetic clinics; all of this has served to increase knowledge about diabetes mellitus. A number of references[1-17] are appended for background reading.

In North America three drugs belonging to two main categories of oral hypoglycemic agents are generally available:

1. *Sulfonylurea agents*: (a) Tolbutamide (Orinase, Mobenol), available in 500-mg. tablets. (b) Chlorpropamide (Diabenese), available in 100-mg. and 250-mg. tablets.

2. *Biguanides*: Phenformin (D.B.I.), available in 25-mg. tablets or more recently as a 50-mg. timed-disintegration capsule allowing gradual release of the drug over a 12-hour period.

MECHANISM OF ACTION

1. *Sulfonylurea agents*: Tolbutamide and chlorpropamide are generally considered to act by stimulating the beta cells of the pancreas to release more insulin, which in turn improves the diabetic state. These agents may also stimulate "mother" beta cells in the islets, which then may divide and produce an increased number of potentially insulin-producing cells.

In order for these drugs to have a beneficial effect, pancreatic beta cells capable of producing insulin must be present in the islets. Thus, they would be useless in a case of total pancreatectomy or in a patient with juvenile diabetes who has no active beta cells.

2. *Biguanides*: In contrast to the sulfonylurea compounds, phenformin is believed to act by increasing peripheral utilization of glucose, *viz.* by increasing intracellular anaerobic glycolysis and by bringing about increased glucose transport across cell membranes with a resultant lowering of the blood sugar. While phenformin has been shown to have blood-sugar-lowering effects in either pancreatectomized animals or those rendered diabetic by destruction of the islets by alloxan, it appears that this drug only acts effectively in the human subject when the patient is producing some insulin of his own or is given insulin by injection.

Thus phenformin is completely different from the sulfonylureas in the manner in which it produces its antidiabetic effects. For this reason it has been used for the oral treatment of patients who had previously been treated with either tolbutamide and/or chlorpropamide without success.

CLINICAL USEFULNESS

These drugs are of proved value in a small group of diabetic patients when used with discrimination. To establish their worth in any one patient, the drug in question must be used on a trial basis. Further, it must be pointed out that the patient must be on a controlled diet, as he must when taking insulin.

In some cases a trial of these agents may be requested by the patient just for the sake of taking an oral agent rather than injections of insulin. It is estimated that about 8% to 10% of diabetics may be controlled on oral agents and diets; thus it is disturbing to read that in the United States about 20% of known diabetics are being given these drugs.

CONTRAINDICATIONS

It is now evident that these agents should not be used as the sole method of treatment in the following patients:

1. Juvenile diabetics.

2. Diabetics under 25 years of age; these patients usually have very little pancreatic reserve and may have wide daily swings in blood sugar concentrations and thus may readily develop ketoacidosis.

3. Older unstable diabetics who have been on diet and insulin, and in whom control has been difficult; these patients rarely do well on these drugs.

4. Patients who have had total pancreatectomy or destruction of the pancreas by inflammatory or neoplastic change.

5. Diabetic patients in the older age groups with infections and/or ketoacidosis will do poorly when given these drugs. Once the infection has been cured and the ketoacidosis is relieved, the use of these agents might be considered.

6. It would seem to be more reasonable to control pregnant diabetics with diet and insulin rather than by the use of oral agents.

INDICATIONS FOR USE

Hence the diabetic patient who is likely to do well on oral therapy is a person of relatively

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normal weight, preferably over the age of 40, with mild diabetes and with an insulin requirement of less than 30 to 40 units daily. If such a person were taken off insulin for a period of time, he would show only moderate glycosuria, a moderate elevation in blood sugar, little or no ketonemia, and very little if any acetone in the urine.

It may be necessary to convert some patients from insulin and diet to oral agents and diet, because of the development of failing eyesight and consequent inability to measure insulin dosage. The only alternative is to arrange for someone to come in and administer the daily insulin, thus adding an additional expense.

These drugs may also be of benefit in some instances of insulin resistance, insulin allergy or insulin fat atrophy, provided the agents effectively control the diabetes.

In patients who have been controlled for some time on insulin and diet and who are progressing favourably, it would seem better not to "rock the boat" by attempting to convert them to the oral agents unless there is a very good reason for so doing.

USE IN EARLY DIABETES

Some interesting observations about these agents have been made, particularly by Loubatières, who wrote some of the original papers on these hypoglycemic drugs. It is known that if tolbutamide is given at the onset of diabetes, it may alter the clinical picture and forestall the development of actual diabetes in a young patient for many months. This same effect has been observed in recently discovered diabetes in older patients. A short course of tolbutamide may result in benefits lasting for some time, and the patients may hence remain free of evidence of the disease on diet alone without tolbutamide or insulin.

OTHER USES

Tolbutamide has been used intravenously to assess insulin-like activity of sera in patients who have hypoglycemia due to other causes.

DOSAGE AND MODE OF ADMINISTRATION

It should be pointed out that tolbutamide and phenformin have a short biological half-life and are given in repeated doses during the day.

Chlorpropamide has a long half-life of 30 to 36 hours and need be given in only one dose during the day. It is believed to be two or three times more potent than tolbutamide.

The usual dosage of these drugs are:

1. Tolbutamide, 500 mg., two to six tablets daily as an initial dose, with a reduction by one tablet a day as control is established. The maintenance dose may be one to four tablets a day. A program which requires more than two tablets a day becomes a financial burden for the average patient.

2. Chlorpropamide, 250 mg., one or two tablets daily; the dosage of two tablets daily should never be exceeded. As control is established, the dosage can often be reduced to one tablet, to a half tablet, to the 100-mg. tablet, or even to 50 mg. a day.

3. Phenformin is available in 25-mg. tablets; treatment is begun with a low dosage of one to two tablets, increased slowly by one tablet every three or four days to a total of eight tablets a day. This may be exceeded occasionally. Possibly the new timed-disintegration capsule will reduce the number of doses required a day, and the side effects.

Phenformin should be given either with the meals or directly after the meals to minimize the side effects.

DRUG OF CHOICE

Tolbutamide is generally used as the drug of choice in initiating therapy. It was one of the first available, is the least toxic and the least productive of side effects.

In the treatment of patients in whom one cannot attain good diabetic control with a reasonable dose of tolbutamide or in whom the beneficial effect seems to be lessening after some time on the drug, one may try chlorpropamide.

This does not imply that either chlorpropamide or phenformin cannot be used as the initial drug. Both of these drugs have been proved to be effective when used as the initial agent, but most clinicians empirically start with tolbutamide, then try chlorpropamide; if these are not successful, they may then use phenformin.

Phenformin has gained the reputation of being useful for the oral treatment of sulfonylurea-resistant diabetes. It has also been used in association with insulin to help smooth out the control of labile "brittle" diabetics. This use with insulin has had varying and often dubious success but may be worth a trial.

CONVERTING FROM INSULIN TO ORAL AGENTS

If one wishes to change over from insulin and diet control in the older patients to oral agents and diet, it may be done readily.

If the patient is taking 30 units of insulin or less a day, the insulin should be discontinued and the patient treated with an adequate amount of one of the sulfonylurea agents just as if he were a new diabetic. If, over the course of two to three weeks, good diabetic control has not been established and acetonuria has appeared, one should then administer insulin again.

With patients who require larger doses of insulin (above 40 units) and in whom a trial of the sulfonylureas is desired, the insulin dose should be decreased by 10 units while a full initial dose of

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the oral drug is being administered. The latter dose is continued while the insulin is decreased by 10 units every two to four days, provided the urine is relatively free of sugar and shows no acetone. If, after two to three weeks, it is found that reasonably good diabetic control cannot be maintained on oral drugs alone, the patient should again be given insulin and the oral therapy abandoned.

ADEQUACY OF CONTROL

In our clinic the following blood sugar levels are used to indicate good control:

Fasting: up to 110 mg. %.
1 hr. p.c.: up to 150 mg. %.
2 hrs. p.c.: up to 130 mg. %.
3 hrs. p.c.: up to 110 mg. %.

Fair control blood sugars are as indicated below:

Fasting: up to 130 mg. %.
1 hr. p.c.: up to 180 mg. %.
2 hrs. p.c.: up to 150 mg. %.
3 hrs. p.c.: up to 130 mg. %.

Patients are seen at the hospital clinic after they have had their breakfast at home and the blood sugar determinations are then made.

It seems more reasonable to accept these "post-breakfast" blood sugar determinations rather than have these patients sit around without breakfast while they wait to be examined by the physician.

It is better to manage the very obese mild diabetic patient by diet alone and see this patient frequently to encourage dieting.

There seem to be a goodly number of older patients in their 60's and 70's at the clinic; we have been inclined to accept slightly higher blood sugar levels in these patients, provided that their weight is reasonable and they have little, if any, glycosuria and usually no acetonuria.

Our impression is that the error most often made by the physician in using sulfonylurea drugs is to start treatment with amounts that are too small. We have seen patients who have been given one tablet of tolbutamide daily; after a month the attending physician says that the drug is of no value to his patient. With the sulfonylureas one has to start with fairly high doses and then decrease the dosage; the reverse is true with phenformin, in which the rule is "start low, go slow".

SIDE EFFECTS AND TOXICITY

Side effects and toxicity occur with all these drugs but are not a major problem if the recommended doses are not exceeded.

Tolbutamide, either Orinase or Mobenol, rarely may cause urticarial reactions, nausea, vomiting and diarrhea as side effects. Other toxic effects have been minimal; the occasional patient with a cholestatic type of jaundice, and more rarely leukopenia, has been reported.

Chlorpropamide (Diabenese) is a more potent drug. Side effects have been encountered more frequently than with tolbutamide, but even so they have been minimal. Urticarial rashes, diarrhea and an occasional hypoglycemic attack have been noted.

A few cases of cholestatic jaundice have been described in the literature and some deaths reported in patients on chlorpropamide. It is felt that if the dosage of two tablets a day, or less, is adhered to and never exceeded, these dangers are considerably reduced.

Over the first six weeks of therapy most of the evidence of toxicity will have been observed and reported; therefore one should be careful to maintain fairly close observation over this period, being particularly alert for hypoglycemia and jaundice. If the patient is not in hospital, he should be seen two to three times a week at first.

Phenformin (D.B.I.) has side effects which have been well documented. They are mainly gastrointestinal upsets, a metallic taste in the mouth, anorexia, nausea and vomiting, and occasionally diarrhea. These may be related to a high initial dosage (which is the incorrect method of initiating the drug) or to giving the tablets between meals. Possibly the new timed-disintegration capsule may help to eliminate these side effects. Toxicity has been practically non-existent.

At times the tendency to develop some degree of acetonuria has been noted in patients who are given both insulin and phenformin despite fairly normal blood sugars and no glycosuria. Urinalyses for acetone should therefore be routinely performed even in the absence of glycosuria.

COMBINATIONS

Although some workers in the field of diabetes have been using combinations of the various agents, it is felt that combined treatment should be conducted only in clinics where advanced experimental observations are being made. It is interesting to read about brittle, older diabetics being controlled on a combination of six tablets of tolbutamide and six to 16 tablets of phenformin. The large number of tablets involved might retard patient co-operation and must be beyond the financial means of the average diabetic patient.

COST

Tolbutamide, as the 500-mg. tablet, costs about 12.5 cents per tablet; chlorpropamide, a 250-mg. tablet, sells at about 12 cents a tablet. Phenformin costs about 7.5 cents a tablet, and the 50-mg. timed-disintegration capsule about 19 cents.

If the patient has to pay more than 30 cents a day for drug therapy, it must generally be considered too high. The average dosage of insulin costs about 10 to 20 cents per day. This has been one of the most commendable features about insulin—that it has been distributed in a most reasonable price range.

THE FUTURE OF ORAL AGENTS

The oral agents have established a place in the treatment of diabetes. Other agents will likely be developed, possibly differing in their action from the present ones. A new, more potent tolbutamide is under investigation by the Upjohn Company, and reports about its efficacy will likely soon appear.

Insulin will not be neglected in the research field and will remain, as it has for 40 years, the bulwark in the treatment of diabetes. The new sulfonated insulins promise to increase the scope of insulin therapy.

It is too soon to say that these drugs will retard or prevent the vascular complications of diabetes mellitus or that there will not be late complications from the drugs themselves.

SUMMARY

Three oral agents have been appraised with regard to their actions, their usefulness, their toxicity and side effects. With due consideration of the indications for use, the correct dosage, and with reasonable supervision of the patient, these can be effective agents in the control of some diabetic patients.

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CASE REPORT

The Shrapnel Awakes:

Pyopneumothorax and Chronic Empyema Resulting from a Foreign Body Retained for 17 Years

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ALTHOUGH foreign bodies may remain in various body cavities and organs for many years without causing trouble, they occasionally produce complications many years after the initial injury. The following case report is of interest because it illustrates a serious intrathoracic complication occurring more than 17 years after a penetrating wound of the chest.

A 37-year-old farmer sustained shrapnel injuries to his leg, hand and chest while serving with the Canadian Armed Forces in France in September 1944. One missile, which entered the right side of the chest in the posterior axillary line, became embedded in the region of the right lung root. The chest wall injury was sutured, but broke down later and finally closed by second intention. No intrathoracic surgery or drainage was carried out, and the patient was invalided home to Canada and discharged six months later.

Over the intervening 17 years he remained well. Several routine chest radiographs taken during this period revealed the metallic foreign body in his right lung root, but no other abnormality. At no time did he have any chest complaints.

On December 29, 1961, he developed a sudden acute pain in his right lower chest, followed by chills, fever and shortness of breath. A chest radiograph on

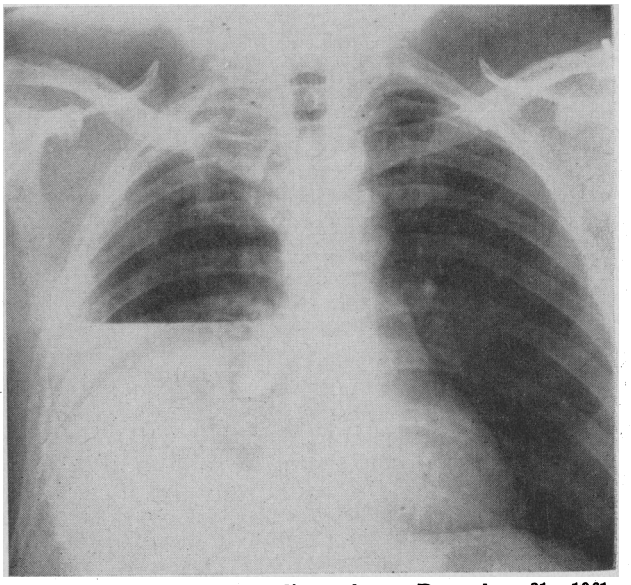

Fig. 1.—Initial chest radiograph on December 31, 1961, revealed a hydropneumothorax with a radio-opaque foreign body in the right hilar region.

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